Patent Docket P1101P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Avi J. Ashkenazi Serial No.: 09/020,746 Filed: February 9, 1998 For: Apo-2 Receptor Antibody	Group Art Unit: 1647 Examiner: C. Kaufman

RULE 131 DECLARATION

I, Avi J. Ashkenazi, hereby declare as follows:

1. I am the named inventor of the claimed subject matter of the above-identified patent application.

2. The above-identified patent application claims priority to application serial no. 08/857,216 filed with the Patent Office on May 15, 1997, and I am the named inventor in that priority application. A copy of my priority application serial no. 08/857,216 (hereinafter the "'216 application") is attached as Exhibit A.

3. All work described in the above-identified application and the '216 application was performed by me or on my behalf in the United States of America.

4. The '216 application filed on my behalf on May 15, 1997 demonstrates both my conception of the claimed invention of the present application and a constructive reduction to practice of the invention.

5. Experiments performed by me or on my behalf relating to the identification and structural characterization of the Apo-2 receptor are described, for example, in Example 1 of the '216 application, pages 58-62. In *in vitro* binding assays, I found that the Apo-2 receptor extracellular domain binds the ligand known as Apo-2 ligand (the '216 application, e.g., pages 63, lines 9-35 - page 64, lines 1-6). In further *in vitro* assays, I also found that the Apo-2 receptor was capable of inducing cell

death in transfected mammalian cells (the '216 application, page 64, lines 9-35 - page 65, lines 1 -13).

6. In the '216 application, agonist antibodies to the Apo-2 receptor are described. (See, e.g., Page 10, lines 3-5; Page 15, lines 7-10; Page 56, lines 21-23). More particularly, the '216 application discloses that an agonistic Apo-2 antibody may be employed to activate or stimulate apoptosis in mammalian cancer cells (Page 56, lines 21-23). Methods for making Apo-2 antibodies are described on pages 48-56 of the '216 application. Apoptotic activity in mammalian cells is described on, e.g., page 17, lines 1-12, of the '216 application.

7. The '216 application therefore demonstrates that agonist antibodies which bind Apo-2 receptor and stimulate apoptosis were conceived and constructively reduced to practice by the May 15, 1997 filing date of my patent application.

8. I have read and reviewed U.S. Patent Application Publication No. 2002/0160446 (corresponding to application serial number 09/811,088, hereinafter the "the '088 application" a copy of which is attached as Exhibit B) which was filed with the Patent Office on March 16, 2001. I understand that the '088 application is a continuation-in-part application of various earlier-filed applications, which include:

- U.S.S.N. 09/757,421 (filed Jan. 10, 2001), now abandoned, which claims priority from U.S.S.N. 08/843,652 (filed Apr. 16, 1997) ("the '652 application"), now abandoned.

I have read and reviewed the '652 application. I note that in these applications, the disclosed and claimed sequences are termed "Tango-63."

9. The '652 application discloses two polynucleotide sequences, called "Tango-63d" and "Tango-63e" that encode a 440 and 411 amino acid sequence, respectively. See, e.g., page 4, lines 20-21. I will refer to these two sequences in this declaration as the "Tango-63" sequences. The '652 application postulates that the Tango-63 sequences are similar to members of the TNF receptor superfamily. See, e.g., page 4, lines 17-19 and page 63, lines 1-3. The '652 application provides no disclosure of any particular sequence-based comparison (such as a sequence alignment) between the Tango-63 sequences and other members of the TNF receptor family. There is a general

statement on page 58, lines 23-25 of the '652 application that there is "conservation" between the intracellular domains of TNFR-1 and Tango-63.

10. The '652 application states that "members of the TNFR receptor superfamily are characterized by the presence of cysteine-rich repeats in their extracellular domains, and the Fas/APO-1 receptor and TNFR-1 also share an intracellular region of homology designated the "death domain"…. See, page 63, lines 4-8. The '652 application does not characterize any particular domains or motifs that may be present in the Tango-63 sequences themselves (e.g., any particular regions of the Tango-63 sequences that may constitute or act as an extracellular domain, intracellular domain or death domain are not described). Accordingly, there is no clear comparison made in the '652 application between the Tango-63 sequences to other known members of the TNF receptor family such as Fas or TNFR-1.

11. The '652 application likewise provides no analysis or data regarding the identity or conservation of specific amino acids within any putative death domain, which were known to be crucial for activity of the death domain of TNFR-1 (see, e.g., Table 2, Tartaglia et al., Cell, 74, 845-853 (1993); Fig. 4B, Brojatsch et al., Cell, 87, 845-855 (1996)).

12. I note that the functional complexity of TNF receptor superfamily members that contain death domain motifs was well known in the art at the time of the filing of the '652 application, particularly with respect to the biological functions associated with binding of ligands to such receptors. One example is the low affinity NGF receptor (p75 NGFR, also called "neurotrophin receptor" or "NTR") known prior to the filing date of the '652 application. In Rabizadeh et al., Science, 261, 345-348 (1993), the authors teach that "expression of p75 NGFR induced neural cell death constitutively when p75 NGFR was unbound; binding by NGF or monoclonal antibody, however, inhibited cell death induced by p75 NGFR". In Chapman, FEBS Lett., 374, 216-220 (1995), the author states that "Unlike TNFR-1 and Fas, cell death induced by NTR (namely p75 NGFR) is reversed rather than caused by ligand binding". Thus, at the time of the filing of the '652 application, binding of ligand to NTR was known to inhibit, rather than stimulate, apoptosis. Therefore, the mere presence of a death domain related sequence is not, standing alone, indicative of the specific function or functions of a receptor in the TNF receptor superfamily, particularly those functions associated with ligand binding to such receptor.

13. The '652 application fails to identify a ligand that specifically binds to the putative receptors encoded by the Tango-63 sequences. Based on my review of the '652 application, it is my belief that the applicant of the '652 application was not aware at the time the application was filed that the Tango-63 bound any specific ligand. See, e.g., page 7, lines 4-11 wherein it states that "...the polypeptides may function in a ligand-independent manner. In the event a ligand is identified, one could then determine whether that ligand acts as a full or partial agonist or antagonist of the polypeptide of the invention...".

14. The '652 application contains no disclosure pertaining to antibodies to the expression products of the Tango-63 sequences that have characteristics of the claimed antibodies of the present application. The disclosure of the '652 application simply provides a general indication that antibodies can be raised to the polypeptides of the invention (see, e.g, page 17, lines 22-24) and can be used in diagnostic or prognostic techniques or in screening assays for the evaluation of the effect of test compounds on expression and/or activity of Tango-63. See, e.g., '652 application at page 33, beginning at line 13 to page 36.

15. There is no description in the '652 application of Tango-63 receptor agonist antibodies which induce apoptosis in mammalian cells. The disclosure refers to "compounds" which may modulate the expression or activity of Tango-63, but such compounds described generally concern, e.g., small molecules, ribozymes, naturally-occuring or synthetic ligand, and anti-sense nucleic acid molecules. See, e.g., page 8, lines 15-26; page 9, lines 4-14; page 10, lines 9-21; page 18, lines 15-26 and page 60, lines 22-28. The '652 application does not describe or suggest such a compound to be an agonist antibody to the Tango-63 sequences. Therefore, it is my opinion that the '652 application neither discloses nor motivates one skilled in the art to make or use an anti-Tango-63 antibody as an agonist antibody that mimicks ligand (i.e., apoptosis-inducing) activity.

16. The '652 application fails to identify or describe any examples of hybridomas or monoclonal antibodies that were actually produced against the Tango-63 sequences. There is likewise no description in the '652 application of any example of a monoclonal antibody that was actually produced which binds

to Tango-63, or which has apoptosis-inducing, or ligand-mimicking, activity.

17. In light of the above facts and observations, it is my opinion that with respect to the '652 application one skilled in the art would find no suggestion to produce antibodies which bind to the putative receptors encoded by the Tango-63 sequences and which induce specific biological functions (e.g., apoptosis) upon binding to these putative receptors.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1/17/03
Date

Avi Ashkenazi
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